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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,752	12/02/2003	Ian Richard Buxton	PU4727US-1	6812

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	**PAPER NUMBER**
1617	

NOTIFICATION DATE	DELIVERY MODE
11/28/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/726,752	BUXTON ET AL.	
	Examiner	Art Unit	
	Umamaheswari Ramachandran	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,36,38,42,45 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,36,38,42,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 9/17/2007 amending claims 34, 36, 38, 42 and adding claims 45 and 46. Claims 1-12, 14-32, 43, 44 are withdrawn from consideration and claims 13, 33, 35, 37, 39-41 are cancelled. Claims 34, 36, 38, 42, 45, 46 are pending.

Response to Remarks

The rejection of claim 13 under 35 U.S.C. 102(b) as being anticipated by Jao et al (U.S. 5,955,103) is withdrawn due to the cancellation of claim 13. The rejection of claim 13 under 35 U.S.C. 102(e) as being anticipated by Nadkarni (WO 03/104192) is withdrawn due to the cancellation of claim 13.Applicants' arguments regarding the rejection of claims 33-42 under 35 U.S.C. 103(a) as being unpatentable over Nadkarni (WO 03/104192) in view of Staniforth (U.S. 5,004,614) have been fully considered but they are not persuasive. The amendments and addition of new claims necessitated the modified rejections given below. The office action is made final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 34, 36, 38, 42, 45, 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nadkarni (WO 03/104192) in view of Staniforth (U.S. 5,004,614) and further in view of Jain et al. (US/ 20020012675, effective filing date Jun 12 1999).

Nadkarni teach rapidly disintegrating multiparticulate controlled release formulations of lamotrigine or a pharmaceutically acceptable salt in a core to provide better control of blood plasma level (see Abstract). Nadkarni further teach a release rate controlling polymer such as poly (methyl methacrylate), poly (ethyl methacrylate) etc (see Abstract, p 6, lines 30-34) in the composition. The reference teaches that the dosage formulation comprises a rate controlling polymer membrane made up of pharmaceutically acceptable polymers such as hydroxypropylmethyl cellulose, polyvinylpyrrolidone, polymers of acrylic and methacrylic acid such as (p 6 lines 27-29). The reference teaches the addition of excipients, diluents such as microcrystalline cellulose, lactose and lubricants such as magnesium stearate (p 9 lines 24-25, p 10, line 8). The reference also teaches Eudragit RL as a suitable polymer (p 31, lines 4-5). The reference further teaches the amount of polymer(s) to be used in forming the particles will be determined based on the amount of drug to be delivered, the drug release rate desired, and the size of the particles and the total amount of the particles including copolymer, filler, plasticizer, excipients and processing aids, are preferably in the range of 5% to 60% weight gain on the cores (p8, lines 9-15). The reference teaches that controlled release lamotrigine, which is designed to avoid excessive Cmax levels will produce lower plasma concentrations, which are reached over a longer period of time (p3, lines 6-7). Nadkarni teach the weight of lamotrigine as 51 % (900 g of lamotrigine added to provide 1750 g of controlled release particles, example 1), and the weight of release retarding polymer such as hydroxypropyl methyl cellulose to be 31% (545.5 g of the polymer added to provide 1750 g of controlled release particles, example 1). The

reference teaches the weight of microcrystalline cellulose to be 57% by weight (493.5 g added to total weight of 867.05 g, example 4) and the lubricants may comprise from 0.05 to 10 weight % of the formulation (p10, lines 1-15).

The reference does not teach the thickness of outer coating or outer coating with one or more orifices.

Staniforth teach a device for controlled release of an active agent, comprising a core comprising an active agent and a release modifying agent; and an outer coating covering said core, the thickness of said coating being adapted such that it is substantially impermeable to the entrance of an environmental fluid present in an environment of use and substantially impermeable to the exit of said active agent during a dispensing period, said coating including an orifice extending substantially completely through said coating but not penetrating said core and communicating from said environment of use to said core for allowing the release of said active agent into said environment of use, said orifice having an area from about 10 to about 60 percent of the face area of said device, the rate limiting step for the release of said active agent substantially being the exit of said active agent through said orifice via one or more of dissolution, diffusion or erosion of said active agent in solution or suspension (col.16, lines 1-24, claim 1). The reference further teaches the drug to be an active agent (col. 5, lines 54-56). The reference teaches diluents such as lactose, fructose etc (col. 5, line 4), magnesium stearate (0.25-5%) weight of the core as a lubricant (col. 5, line 19) and hydroxypropylmethyl cellulose for thick coatings of the polymeric materials (col. 6, lines 60-65). The reference teaches that the thickness of the coating necessary to provide

results in accordance may be simply determined by one of ordinary skilled in the art via the preparation of devices with differing coating thicknesses, performing dissolution tests in the devices without the inclusion of an orifice in the device, and choosing the coating thickness which does not allow the release of the active agent from the device during the desired duration of controlled release (col. 7, lines 3-13). The reference further teaches that release-modifying agents may be used to slow the release of active agent from the device and examples of such agents include insoluble polymers.

The references do not explicitly teach the outer coat dissolve when the surrounding pH exceeds 5.

It would have been obvious to one of ordinary skill in the art at the time of the invention that the outer coat of sustained formulation of lamotrigine dissolves when the surrounding pH exceeds 5 because Nadkarni teach rapidly disintegrating multiparticulate controlled release formulations of lamotrigine and the rate-controlling membrane is made up of pharmaceutically acceptable polymer(s) of varying water solubility or water permeability and further teach an especially preferred embodiment, the rate controlling polymers contain methacrylate co-polymers such as Eudragit RL and Eudragit RS. The reference further teaches that Eudragit RL is highly permeable and Eudragit RS and Eudragit NE 30D low permeable polymers, independent of pH and Eudragit L is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester, it is insoluble in acids and pure water and it becomes soluble in neutral to weakly alkaline conditions and the permeability of Eudragit L. is pH dependent. The reference teaches that above pH 5.0, the Eudragit L polymer becomes increasingly

permeable. (Eudragit L is described in the "Eudragit L" brochure of Rohm Pharma GmbH (1986)) (see p 6 lines 23 –33, p 7 lines 1-14). Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to use an outer coat polymeric material based on the desired pH as Eudragit L is pH dependent and becomes increasingly permeable about pH 5.0 and Eudragit RL is highly permeable and Eudragit RS and Eudragit NE 30D low permeable polymers, independent of pH. Also, it would have been obvious to one of ordinary skill in the art that the outer coat may dissolve when the surrounding pH exceeds 5 because the physiological pH is 6.8-7.4 and when lamotrigine is administered orally one can expect the dissolution of the outer coat in the stomach as the physiological pH exceeds 5. Also, One of ordinary skill in the art would be motivated to use the appropriate pH that would simulate in vivo conditions to get an idea of how the composition would behave in the human body. It is within the level of ordinary skill in the art to manipulate the formulation and pH parameters to achieve the desired release profile over a range of pH environments.

It would have been obvious to one of ordinary skill in the art at the time of the invention to make a sustained release formulation of lamotrigine with an outer coat covering said core impermeable to environmental fluids because of the teachings of Nadkarni and Staniforth. Nadkarni teaches that the advantage of controlled release of a drug is to provide therapeutically effective level of an agent for an extended period of time and longer period of pharmacological and diagnostic response and teaches sustained release formulation of lamotrigine. Staniforth teaches a different technique of controlled release formulation of drugs by adjusting the thickness of the outer coating so

that it is substantially impermeable to the entrance of an environmental fluid present in an environment of use and substantially impermeable to the exit of said active agent during a dispensing period. Hence one of ordinary skill in the art would have been motivated to combine the teachings of Nadkarni with Staniforth to provide a sustained release formulation of lamotrigine with an outer coating that is impermeable to environmental fluid and impermeable to the exit of an active agent such as lamotrigine.

The references do not explicitly teach the rate-retarding polymer as HPMC.

Jain et al. teach controlled release nanoparticulate formulations comprising a nanoparticulate agent to be administered and a rate-controlling polymer. Jain et al. teach lamotrigine as one of the agents and hydroxypropyl methylcellulose (HPMC) as one of the release retarding polymers (see Abstract, para 0047, 0056).

It would have been obvious to one of ordinary skill in the art at the time of the invention to add a release-retarding agent such as HPMC in a controlled release formulation comprising lamotrigine because of the teachings of Staniforth and Jain. One of ordinary skill in the art would have been motivated to do so because Staniforth teach it may be advantageous to include one or more release modifying agents in the tablet core which aids in the release of the active agent from the device in the environment of use and Jain teaches HPMC as one of the particularly useful rate-controlling polymers for causing an effective controlled release of administered drug or agent following administration.

The reference does not teach a value for the thickness of the outer coat polymer as claimed in claim 38 of the instant application.

It would have been obvious to one of ordinary skill in the art at the time of the invention to make an outer coat of the formulation of lamotrigine with 0.05-0.30 mm of polymer. The motivation to do so is provided by Staniforth's teachings. The reference clearly teaches that the thickness of the coating necessary to provide results in accordance may be simply determined by one of ordinary skilled in the art via the preparation of devices with differing coating thicknesses, performing dissolution tests in the devices without the inclusion of an orifice in the device, and choosing the coating thickness which does not allow the release of the active agent from the device during the desired duration of controlled release (col. 7, lines 3-13). Hence one of ordinary skill in the art would have been able to adjust the thickness of the outer coat of the sustained formulation of lamotrigine by routine experimentation as Staniforth teaches the controlled release device having a core and an outer coating and the outer coating polymer materials and examples to make the formulation.

The reference does not teach the AUC values or the Cmax values after administration of sustained release formulation of lamotrigine as in claim 42.

It would have been obvious to one of ordinary skill in the art that the sustained formulation comprising lamotrigine having a Cmax less than the instant release tablet containing the same amount of lamotrigine because Nadkarni teaches that the controlled release lamotrigine, which is designed to avoid excessive Cmax levels will produce lower plasma concentrations, which are reached over a longer period of time. Also, it is obvious to one of ordinary skill in the art that the sustained release formulation

comprising the same composition taught by the teachings of Nadkarni and Staniforth will have same release profile and the properties such as AUC and Cmax values.

Response to Arguments

Applicants' argue that Applicants' claimed invention does not use a rapidly disintegrating binder for dispersion as required by Nadkarni. In response, the claims of the instant invention do not have such a limitation and claim 34 is directed a sustained releasing formulation of lamotrigine comprising a core.

Applicants' argue that the instant invention is formulated with attention to the stomach and intestine environments and not to the water/suspension environment as Nadkarni's and Applicant's formulation has an outer coating and orifice(s). In response, the claims of the instant invention do not have any limitations that the formulation of lamotrigine is directed to stomach and intestine environments. Nadkarni teach a formulation comprising lamotrigine and an outer coat with the same polymers (such as Eudragit) as the instantly claimed invention. Staniforth et al. is used to teach that a controlled release formulation can be made with a core containing an active drug and the outer coat with orifices and the rate of the release of the drug being controlled with orifices. Thus combined teachings Nadkarni and Staniforth's are obvious over the instantly claimed pharmaceutical formulation.

Applicants' argue that neither Staniforth and Nadkarni teach an outer coating that dissolves at pH above 5. In response, Nadkarni does not explicitly teach that the outer coat dissolves at pH above 5. However, Nadkarni teach a controlled release formulation of lamotrigine with an outer coat made of the same polymers as the instantly claimed

application. The properties are inseparable from a compound and therefore, if the prior art teaches the identical chemical structure, the properties Applicant discloses and/or claims are necessarily present. In addition, as stated above, Nadkarni teach the rate-controlling membrane is made up of pharmaceutically acceptable polymer(s) of varying water solubility or water permeability and further teach an especially preferred embodiment, the rate controlling polymers contain methacrylate co-polymers such as Eudragit RL and Eudragit RS. The reference further teaches that Eudragit RL is highly permeable and Eudragit RS and Eudragit NE 30D low permeable polymers, independent of pH and Eudragit L is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester, it is insoluble in acids and pure water and it becomes soluble in neutral to weakly alkaline conditions and the permeability of Eudragit L. is pH dependent. The reference teaches that above pH 5.0, the Eudragit L polymer becomes increasingly permeable. (Eudragit L is described in the "Eudragit L" brochure of Rohm Pharma GmbH (1986)) (see p 6 lines 23 –33, p 7 lines 1-14). Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to use an outer coat polymeric material based on the desired pH as Eudragit L is pH dependent and becomes increasingly permeable about pH 5.0 and Eudragit RL is highly permeable and Eudragit RS and Eudragit NE 30D low permeable polymers, are independent of pH.

Conclusion

Applicant's amendment necessitated the modified rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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SHEENI PADMANABHAN
SUPERVISORY PATENT EXAMINER